Journal of Medical Virology 57:111–113 (1999)

Heterosexual Transmission of Hepatitis C in Italy

Alfonso Mele,[1] Tommaso Stroffolini,[1]* Maria Elena Tosti,[1] Rosamaria Corona,[2] Franco Santonastasi,[3] Giovanni Gallo,[4] Pietro Ragni,[5] Emanuela Balocchini,[6] Rossana Bernacchia,[7] and Angela Moiraghi[8]

[1]*Laboratory of Epidemiology, Istituto Superiore di Sanità, Roma, Italy*
[2]*Servizio Epidemiologia, Istituto Dermopatico dell'Immacolata, Roma, Italy*
[3]*Assessorato alla Sanità, Regione Campania, Italy*
[4]*Assessorato alla Sanità, Regione Veneto, Italy*
[5]*Assessorato alla Sanità, Regione Emilia Romagna, Italy*
[6]*Assessorato alla Sanità, Regione Toscana, Italy*
[7]*Assessorato alla Sanità, Regione Marche, Italy*
[8]*Dipartimento di Igiene e Medicina Preventiva, Università di Torino, Torino, Italy*

Data from a surveillance system for type-specific acute viral hepatitis in Italy has been used to evaluate the risk of heterosexual transmission of hepatitis C virus (HCV) associated with sexual activity with multiple partners in subjects ≥15 years of age. Hepatitis A cases were used as controls. During the period 1991–1996, 1,359 acute hepatitis C and 4,365 hepatitis A cases were recorded among subjects ≥15 years of age. Intravenous drug use was the most frequent source of infection (35.9%) reported by HCV cases; two or more sexual partners during the 6 months before disease onset accounted for 34.9% of hepatitis C cases. Adjusting by multiple logistic regression analysis for the confounding effect of all risk factors considered (blood transfusion, intravenous drug use, surgical intervention, dental therapy, other parenteral exposure), and for age, sex, area of residence, and educational level of subjects, showed that having two or more sexual partners is an independent predictor of the likelihood of hepatitis C (OR = 2.2; 95% CI = 1.7–2.7). After excluding intravenous drug users and patients transfused with blood from analysis, the increase in the adjusted OR for the association between HCV and the number of sexual partners correlated with the increase in the number of sexual partners. The risk of hepatitis C was 2.0 times higher (95% CI = 1.4–2.9) for subjects with two sexual partners and 2.8 times higher (95% CI = 2.1–3.8) for subjects with three or more sexual partners, as compared to subjects with less than two sexual partners. These findings suggest that heterosexual transmission may play an important role in the spread of hepatitis C in Italy. ***J. Med. Virol. 57:111–113, 1999.*** © 1999 Wiley-Liss, Inc.

KEY WORDS: hepatitis C transmission; epidemiology of hepatitis C

INTRODUCTION

A number of bloodborne viral infections (e.g., human immunodeficiency virus (HIV), hepatitis B) may be transmitted between partners during sexual intercourse. Epidemiological evidence for sexual transmission of non-A, non-B hepatitis has been provided [Alter et al., 1989]. Sexual transmission of hepatitis C virus (HCV) has not been firmly established. Studies performed on this topic have been cross-sectional or retrospective, providing conflicting results [Kao et al., 1992; Bresters et al., 1993; Hallam et al., 1993; Honda et al., 1993; Osmond et al., 1993a; Weinstock et al., 1993; Akahane et al., 1994; Chang et al., 1994; Thomas et al., 1994]. However, due to the cross-sectional or retrospective nature of these studies, results may have been inflated, to some extent, by bias.

A recent prospective study measured directly the magnitude of the risk of sexual transmission in the partners of anti-HCV–positive subjects. The data showed a seroconversion rate of 12 cases per 1,000 person/year of exposure [Piazza et al., 1997].

In 1985, a specific surveillance system for acute viral hepatitis (SEIEVA) in Italy was developed [Mele et al., 1986]. Using data from SEIEVA, the risk of heterosexual transmission of hepatitis C associated with sexual activity with multiple partners was evaluated.

MATERIALS AND METHODS

SEIEVA was started in Italy in 1985, coordinated by the Istituto Superiore di Sanità in collaboration with

Grant sponsor: Viral Hepatitis Project, Istituto Superiore di Sanità; grant number: 30/12/1992 n. 502.

*Correspondence to: Dr. Tommaso Stroffolini, Laboratory of Epidemiology, ISS, Viale Regina Elena, 299, 00161 Roma, Italy.

Accepted 8 April 1998

TABLE I. Sociodemographic Characteristics of the Study Population[a]

Characteristics	Hepatitis C (n = 1359) n	%	Hepatitis A (n = 4365) n	%
Sex				
Male	941	69.5	2860	65.6
Female	413	30.5	1497	34.4
Age				
15–24	447	32.9	2239	51.3
25–34	449	33.0	1316	30.1
≥35	463	34.1	810	18.6
Education level				
<8 years	922	67.8	2153	49.3
≥8 years	437	32.2	2212	50.7
Geographic area				
North center	1033	76.0	2440	55.9
South islands	326	24.0	1925	44.1

[a]Subjects ≥15 years of age. SEIEVA, 1991–1996.

local health districts (USLs). From 1985 to 1996, the number of health districts participating in SEIEVA has greatly increased, covering about 46% of the Italian population (129 districts in 1996). SEIEVA uses weekly notification of cases and a two-page standard questionnaire for data collection on risk factors.

Case definition is based on clinical and serological criteria. The clinical criteria are acute illness compatible with hepatitis and serum aminotransferase (ALT) levels greater than 2.5 times the normal upper limit. The serological criteria used to distinguish the different types of hepatitis are as follows: hepatitis A is defined as IgM anti-HAV–positive (regardless of HBsAg status); hepatitis B as HbsAg-positive and IgM anti-HAV–negative or not done (IgM anti-HBc positivity was added in 1987); non-A–non-B hepatitis as IgM anti-HAV–negative and HbsAg-negative; non-A–non-B hepatitis cases with a positive test for anti-HCV are labeled as hepatitis C.

Assays for hepatitis markers are performed in different laboratories in various part of the country. Most acute hepatitis cases were hospitalized, and virtually all hospitalized cases are recorded by the health districts. No changes were made in the notification system during the period considered.

Statistical Analysis

To estimate the association of hepatitis C cases with the potential risk factors, hepatitis A cases were used as controls. The crude odds ratios (OR), which are estimates of relative risk, and their 95% confidence intervals (CI), for the factors under consideration were calculated in univariate analysis. To identify independent predictors of hepatitis C, the adjusted OR were calculated by multiple logistic regression analysis [Breslow and Day, 1980]. Age, sex, area of residence, and educational level were also adjusted for in the analysis.

The aim of the present study was to evaluate the risk of acquiring hepatitis C for subjects with multiple heterosexual partners; analysis was therefore restricted to subjects ≥15 years of age.

RESULTS

During the period 1991–1996, 1,359 acute HCV and 4,365 acute HAV cases were recorded among subjects ≥15 years of age. Sociodemographic characteristics of HCV and HAV cases are shown in Table I. The frequency of risk factors reported by HCV and HAV cases (control group), the crude OR estimated by univariate analysis, and the adjusted OR derived from multiple logistic regression analysis are presented in Table II. Intravenous drug use was the most frequent source of infection (35.9%) reported by HCV cases; two or more sexual partners during the 6 months before disease onset accounted for 34.9% of hepatitis C cases. Adjusting for the confounding effect of all parenteral risk factors considered and for age, sex, area of residence, and educational level of the subjects showed that having two or more sexual partners is an independent predictor of the likelihood of hepatitis C (OR = 2.2; CI 95% = 1.7–2.7).

After excluding intravenous drug users and patients transfused with blood from analysis, the increase in the adjusted OR for the association between HCV and the number of sexual partners correlated with the increase in the number of sexual partners. The risk of hepatitis C was 2.0 times higher (95% CI = 1.4–2.9) for subjects with two sexual partners and 2.8 times higher (95% CI = 2.1–3.8) for subjects with three or more sexual partners, as compared to subjects with less than two sexual partners (Table III).

DISCUSSION

This is one of the very few studies focusing on acute hepatitis C cases, in whom a limited period of previous

TABLE II. Frequency of Reported Risk Factors Among Acute HCV+ and Acute HAV+ Cases (Controls) During the Six Months Before Disease Onset[a]

Risk factors	Hepatitis C n = 1,359	%	Hepatitis A n = 4,365	%	OR_{crude} (95% CI)	$OR_{adjusted}$ (95% CI)
Blood transfusion	36	2.8	19	0.5	6.1 (3.4–11.1)	3.0 (1.4–6.4)
Intravenous drug use	470	35.9	87	2.2	25.4 (19.9–32.6)	36.5 (26.7–49.9)
Surgical intervention	206	16.1	167	4.2	4.4 (3.5–5.5)	3.5 (2.6–4.7)
Dental therapy	348	26.9	852	21.1	1.3 (1.2–1.6)	1.4 (1.1–1.7)
Other parenteral exposure[b]	389	31.0	842	23.4	1.5 (1.3–1.7)	1.3 (1.0–1.5)
>1 sexual partner	398	34.9	514	17.0	2.6 (2.2–3.1)	2.2 (1.7–2.7)

[a]Crude and adjusted OR. Subjects ≥15 years of age. SEIEVA 1991–1996.
[b]Ear piercing, tattooing, acupuncture, attendance at a chiropodist, manicurist, or barber shop.

TABLE III. Number and Frequency (%) of Sexual Partners Reported by Hepatitis C Cases and Hepatitis A Cases Within the Previous Six Months[a]

Number of sexual partners	Hepatitis C n	Hepatitis C %	Hepatitis A n	Hepatitis A %	OR_{crude} (95% CI)	$OR_{adjusted}$ (95% CI)
0–1	531	75.4	2467	83.8	1.0	1.0
2	63	8.9	193	6.6	1.5 (1.1–2.1)	2.0 (1.4–2.9)
≥3	110	15.6	284	9.6	1.8 (1.4–2.3)	2.8 (2.1–3.8)

[a]Subjects ≥15 years of age. Intravenous drug users and blood transfused patients have been excluded. Crude and adjusted odds ratios. SEIEVA, 1991–1996. Adjusted for sex, age, educational level, geographic area, surgical intervention, dental therapy, and other parenteral exposures.

exposure (6 months) has been investigated. Thus, any potential recall bias has been minimized.

Studies assessing the risk of heterosexual transmission of HCV have mostly focused on sexual partners of individuals with chronic HCV infection [Kao et al., 1992; Bresters et al., 1993; Hallam et al., 1993; Osmond et al., 1993a; Akahane et al., 1994; Chang et al., 1994]. In some studies, the lifetime number of sexual partners or history of other sexually transmitted diseases has been retrospectively analyzed [Weinstock et al., 1993; Thomas et al., 1994] in subjects with chronic HCV infection as an indirect indication of the risk of acquiring HCV infection by sexual transmission.

Hepatitis A cases in the present study were used as controls to estimate the strength of association between hepatitis C and heterosexual activity with multiple partners. Hepatitis A and hepatitis C have different modes of transmission. In case control studies, comparability is more important than representation. In this study, hepatitis A and hepatitis C patients were notified cases identified through the same surveillance system and therefore exposed to similar selective factors, if any. In addition, the influence of confounders such as age, sex, area of residence, educational level of subjects, and parenteral exposures has been removed by logistic regression analysis.

The results suggest that heterosexual activity with multiple partners is associated with an increased risk of acquiring hepatitis C; moreover, the risk increases with increased number of sexual partners. These findings are in agreement with the results of a recent Spanish study, which showed that pregnant hepatitis C seropositive women with a history of 2–4 partners other than the regular partnership had a 2.8-fold risk of HCV infection as compared with women who did not engage in extramarital sexual activity; more than four sexual partners increased the risk by at least eightfold [Salleras et al., 1997].

Although the efficiency of sexual transmission of HCV is lower than that of HBV [Melbye et al., 1990; Osmond et al., 1993b], the number of persons who may acquire HCV infection through this route may not be negligible, given the rate of sexual activity among the general population. The findings provided above suggest that heterosexual transmission may play an important role in the spread of hepatitis C in Italy.

ACKNOWLEDGMENTS

The authors thank Antonella Marzolini for assistance.

REFERENCES

Akahane Y, Kojima M, Sugai V, Sakamoto M, Miyazaki Y, Tanaka T. 1994. Hepatitis C virus infection in spouses of patients with type C chronic liver disease. Ann Int Med 120:748–752.

Alter MJ, Coleman PJ, Alexander T, Kramer E, Miller JK, Mandel F. 1989. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. J Am Med Assoc 262: 1202–05.

Breslow NE, Day NE. 1980. Statistical methods in cancer research. I. The analysis of case-control studies. IARC Sci Pub 32:5–338.

Bresters D, Mauser-Bunschoten EP, Reesink HW. 1993. Sexual transmission of hepatitis C virus. Lancet 342:210–211.

Chang TT, Lion TC, Young KC, Lin XZ, Lin CY, Shin JS. 1994. Intrafamilial transmission of hepatitis C virus: The important role of inapparent transmission. J Med Virol 42:91–96.

Hallam NF, Fletcher ML, Read SJ, Majid AM, Kurtz JB, Rizza CR. 1993. Low risk of sexual transmission of hepatitis C virus. J Med Virol 40:251–253.

Honda M, Kaneko S, Unoura M, Kobayashi K, Murakami S. 1993. Risk of hepatitis C virus infections through household contact with chronic carriers: Analysis of nucleotide sequences. Hepatology 17: 971–976.

Kao JH, Chen PJ, Yang PH. 1992. Intrafamilial transmission of hepatitis C virus: The important role of infection between spouses. J Inf Dis 166:900–903.

Melbye M, Biggar RJ, Wantzin P, Krogsgaard K, Ebbesen P, Becker NG. 1990. Sexual transmission of hepatitis C virus: Cohort study (1981–1989) among European homosexual men. Br Med J 301:210–212.

Mele A, Rosmini F, Zampieri A, Gill ON. 1986. Integrated epidemiological system for acute viral hepatitis in Italy (SEIEVA): Description and preliminary results. Eur J Epidemiol 2:300–304.

Osmond DH, Padian NS, Sheppard HW, Glass S, Sihboski SC, Reingold A. 1993a. Risk factors for hepatitis C virus seropositivity in heterosexual couples. J Am Med Assoc 269:361–365.

Osmond DH, Charlebois E, Sheppard HW, Page K, Winkelstein W, Moss AR, Reingold AR. 1993b. Comparison of risk factors for hepatitis C and hepatitis B virus infection in homosexual men. J Inf Dis 167:66–71.

Piazza M, Sagliocca L, Tosone G, Guadagnino V, Stazi MA, Orlando R, Borgia G, Rosa D, Abrignani S, Palumbo F, Manzin A, Clementi M. 1997. Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin. Arch Int Med 157:1537–1544.

Salleras L, Bruguera M, Vidal J, Plans P, Dominguez A, Salleras M, Navas E, Galì N. 1997. Importance of sexual transmission of hepatitis C virus in seropositive pregnant women: A case-control study. J Med Virol 52:164–167.

Thomas DL, Cannon RO, Shapiro CN, Hook EW III, Alter MJ, Quinn TC. 1994. Hepatitis C, hepatitis B and human immunodeficiency virus infections among non-intravenous drug-using patients attending clinics for sexually transmitted diseases. J Inf Dis 169:990–995.

Weinstock HS, Bolan G, Reingold AL, Polish LB. 1993. Hepatitis C infection among patients attending a clinic for sexually transmitted diseases. J Am Med Assoc 269:392–394.